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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,780	08/30/2001	Kevin P. Baker	P2548P1C10	2570

28442 7590 07/15/2005

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EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/943,780

Applicant(s)

BAKER ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

5-0-0

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/27/05 has been entered.
2. Claim 33 has been amended.
Claims 1-26, 35-36 have been canceled.
3. Claims 27-34 are pending and under examination.
4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
5. This Office Action contains NEW GROUNDS of rejections.

Specification

6. The disclosure is objected to because of the following informalities:
 - A. The first line of the specification needs to indicate that applications 09/216021, 09/218517, and 09/254311 are abandoned.Appropriate correction is required.

Rejections Withdrawn

7. The rejection of claims 25-26, 33-34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendments to the claims.

8. The rejection of claims 25-26, 35-36 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

9. The rejection of claims 27-34 under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility is maintained.

The response filed 4/27/05 has been carefully considered but is deemed not to be persuasive. The response states that the Office rejects the evidence submitted by applicants and argues that the evidence as well as the Pennica reference cited by the Examiner demonstrates the unpredictability in the art (see page 8 of response) and the response cites a new Hu reference and argues that the entirety of the Orntoft reference

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would lead to one skill in the art not questioning Applicants assertion of utility (see page 10-11 of response).

In response to this argument, again while some references demonstrate production of the protein from mRNA, numerous examples were cited by the examiner as well as some from applicant for unpredictability and thus, it appears that the art is unpredictable and the only nucleic acid that is overexpressed in tumor is SEQ ID NO:68 and there is no indication that the polypeptide of SEQ ID NO:69 is overexpressed in tumors.

The prior art cited by the examiner also showed the unpredictability in the art as far as protein expression correlated with mRNA levels and it appears from the prior art that each gene expression analysis must be performed in order to determine definitively whether protein correlates with mRNA levels. In addition, it appears that the half-life of the protein is important for use as a diagnostic marker and if a short half-life this would add to the unpredictability of using SEQ ID NO:69 as a diagnostic marker.

The response further states that in the Pennica et al reference because the RNA expression in one of the genes might be inaccurate this result should be disregarded (see page 11 of response). In response to this argument, again Pennica demonstrates that each gene amplification and correlation to protein overexpression needs to be determined by a case by case basis because even Pennica's three gene expression do not correlate and one skill in the art would not disregard the data in a paper just because it did not confirm ones theory.

The response then argues that the utility is that the PRO357 can be used in competitive binding assays with ALS (see page 12 of response). This asserted utility is based on the homology PRO357 shares with ALS and cites references of conservative elements in proteins (see page 13-14 of response). In response to this argument, the assertion that the disclosed protein has biological activities similar to known insulin-like growth factors is not credible in the absence of supporting evidence, because the relevant literature reports (cited in a previous Office Action) numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF- β 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- β family (1987, Cell 49:437-8, esp. p. 438,

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column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in

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Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three-dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of growth factor activity.

Thus, in view of the above discussion the claims remain rejected under lack of a substantial utility.

10. The rejection of claims 27-34 rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained.

The response filed 4/27/05 has been carefully considered and is deemed not to be persuasive. The response states that the claimed polypeptides have utility as stated

above (see page 15-16 of response). In response to this argument, the remarks above address the rejection of 101 and as such one would not know how to use the claimed invention.

11. The rejection of claims 27-34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 4/27/05 has been carefully considered but is deemed not to be persuasive. The response states that applicants have canceled claims 25-26 and this overcomes the rejection (see page 16 of response).

In response to this argument, claims 27-34 still have an enablement problem as indicated previously for unpredictability in the art for expression of mRNA does not necessarily correlates not predicts polypeptide expression and the prior art cited by the examiner also showed the unpredictability in the art as far as protein expression correlated with mRNA levels and it appears from the prior art that each gene expression analysis must be performed in order to determine definitively whether protein correlates with mRNA levels.

In view of the lack of guidance, lack of examples, and lack of predictability in the art as evidenced from the above references, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

The following are NEW GROUNDS of rejections

Priority

12. It is acknowledged that applicants have updated their priority statement in the first line of the specification. However, because of the lengthy priority and the numerous applications claimed, it is unclear where support for the claims are found. It is noted that applications 09/216021 and 09218517 do not have SEQ ID NO:69 in them, therefore, there is no support in these applications. In addition, the following PCT applications were no longer pending when '780 was filed:

PCT/US98/19330

PCT/US98/25108

PCT/US99/12252

PCT/US99/28409

PCT/US99/28313

PCT/US99/28301

PCT/US99/30095

For the PCT applications listed below, in order for the priority claim to be valid, a demand would have had to of been filed to provide for a 30-month pendency. The office cannot verify this because in each case, the EP was the ISA, and no demand was filed with the IPEA/US. Therefore, The Office requests applicant to provide

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documentary proof that a demand was timely filed with the IPEA/EP for the following

PCTs:

PCT/US99/21090

PCT/US00/03565

PCT/US00/04414

PCT/US00/05841

PCT/US00/08439

PCT/US00/14042

PCT/US00/20710

PCT/US00/32678

In addition, it is requested that support be pointed out for each application claimed for priority. Because it is not clear where support is found, the priority for the claims is granted to 5/25/01 wherein the 09/866,028 application has support for the claims. Applicant is reminded that the claimed polypeptide rely on the gene amplification assay for utility and such priority for the instant claim limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 27-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Botstein et al (WO 99/35170, published 7/15/99).

The claims recite an isolated polypeptide of SEQ ID NO:69 and comprising a polypeptide lacking the signal peptide and comprising the extracellular domain and wherein the sequence is in cDNA of ATCC 209527 and the polypeptide is fused to an epitope tag.

Botstein et al teach PRO357 or SEQ ID NO:16 which is identical to SEQ ID NO:69 in the instant application as well as epitope tags and since the claims recite comprising the teaching of the entire PRO357 reads on the claims (see entire document especially page 23).

Conclusion

15. No claim is allowed.


16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or

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filed papers or relating to the status of this application or proceeding should be directed to the Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827


LARRY R. HELMS, PH.D
PRIMARY EXAMINER


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PRIMARY EXAMINER